IN THE CLAIMS

Please replace the claims as filed with the claims set forth below. This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently Amended) An oncolytic herpes simplex virus wherein the herpes simplex virus genome comprises nucleic acid encoding an heterologous nitroreductase (NTR),

wherein the genome has an inactivating mutation in the RL1 locus such that the herpes simplex virus does not produce a functional ICP34.5 gene product,

and wherein the herpes simplex virus is a mutant of one of HSV-1 strains 17 or F or HSV-2 strain HG52.

2. (Previously Presented) The herpes simplex virus as claimed in claim 1 wherein said NTR is E.coli NTR.

3. (Currently Amended) The herpes simplex virus as claimed in claim 2 wherein said nucleic acid comprises ~~SEQ ID No.~~ SEQ ID NO: 2 or nucleic acid encoding the polypeptide of ~~SEQ ID No.~~ SEQ ID NO: 1.

4. (Currently Amended) The herpes simplex virus as claimed in claim 1 wherein said nucleic acid:

(a) has at least 90% ~~60%~~ sequence identity to ~~SEQ ID No.~~ SEQ ID NO: 2 or to a nucleic acid encoding the polypeptide of ~~SEQ ID No.~~ SEQ ID NO: 1, wherein said nucleic acid encodes a protein that has nitroreductase activity;.

~~(b) has at least 70% sequence identity to SEQ ID No. 2 or to a nucleic acid encoding the polypeptide of SEQ ID No. 1; or~~

~~(c) hybridises to the nucleic acid of SEQ ID No. 2, to its complement or to a nucleic acid encoding the polypeptide of SEQ ID No. 1 under high stringency conditions.~~

5.-6. (cancelled)

7. (Previously Presented) The herpes simplex virus of claim 1 wherein said herpes simplex virus genome further comprises a regulatory nucleotide sequence operably linked to said nucleic acid encoding NTR, wherein said regulatory nucleotide sequence has a role in controlling transcription of said NTR.

8. (Previously Presented) The herpes simplex virus of claim 1 wherein said nucleic acid is located in at least one RL1 locus of the herpes simplex virus genome.

9. (Previously Presented) The herpes simplex virus of claim 1 wherein said nucleic acid is located in, or overlaps, at least one of the ICP34.5 protein coding sequences of the herpes simplex virus genome.

10. (Cancelled)

11. (Previously Presented) The herpes simplex virus of claim 1 wherein the herpes simplex virus is a mutant of HSV-1 strain 17 mutant 1716.

12. (Previously Presented) The herpes simplex virus of claim 1 which is a gene specific null mutant.

13. (Previously Presented) The herpes simplex virus of claim 1 which is an ICP34.5 null mutant.

14. (Previously Presented) The herpes simplex virus of claim 1 which lacks at least one expressible ICP34.5 gene.

15. (Previously Presented) The herpes simplex virus of claim 1 which lacks only one expressible ICP34.5 gene.

16. (Previously Presented) The herpes simplex virus of claim 1 which is non-neurovirulent.

17. (Previously Presented) The herpes simplex virus of claim 1 wherein said nucleic acid encoding the heterologous nitroreductase (NTR) forms part of a nucleic acid cassette integrated in the genome of said herpes simplex virus, said cassette encoding:

(a) said nucleic acid encoding NTR; and nucleic acid encoding

(b) a ribosome binding site; and

(c) a marker,

wherein the nucleic acid encoding NTR is arranged upstream (5') of the ribosome binding site and the ribosome binding site is arranged upstream (5') of the marker.

18. (Previously Presented) The herpes simplex virus according to claim 17 wherein a regulatory nucleotide sequence is located upstream (5') of the nucleic acid encoding NTR, wherein the regulatory nucleotide sequence has a role in regulating transcription of said nucleic acid encoding NTR.

19. (Previously Presented) The herpes simplex virus according to claim 17 wherein the cassette disrupts a protein coding sequence resulting in inactivation of the respective gene product.

20. (Previously Presented) The herpes simplex virus of claim 17 wherein a transcription product of the cassette is a bi- or poly- cistronic transcript comprising a first cistron encoding the NTR and a second cistron encoding the marker wherein the ribosome binding site is located between said first and second cistrons.

21. (Previously Presented) The herpes simplex virus of claim 17 wherein the ribosome binding site comprises an internal ribosome entry site (IRES).

22. (Previously Presented) The herpes simplex virus of claim 17 wherein the marker is a defined nucleotide sequence encoding a polypeptide.

23. (Previously Presented) The herpes simplex virus as claimed in claim 22 wherein the marker comprises the Green Fluorescent Protein (GFP) protein coding sequence or the enhanced Green Fluorescent Protein (EGFP) protein coding sequence.

24. (Previously Presented) The herpes simplex virus of claim 17 wherein the marker comprises a defined nucleotide sequence detectable by hybridisation under high stringency conditions with a corresponding labelled nucleic acid probe.

25. (Previously Presented) The herpes simplex virus of claim 17 wherein the cassette further comprises nucleic acid encoding a polyadenylation sequence located downstream (3') of the nucleic acid encoding the marker.

26. (Previously Presented) The herpes simplex virus as claimed in claim 25 wherein the polyadenylation sequence comprises the Simian Virus 40 (SV40) polyadenylation sequence.

27.-30. (cancelled)

31. (Withdrawn) A method of lysing or killing tumour cells *in vitro* or *in vivo* comprising the step of administering to a patient in need of treatment the herpes simplex virus of claim 1.

32. (Previously Presented) A medicament, pharmaceutical composition or vaccine comprising the herpes simplex virus of claim 1.

33. (Previously Presented) The medicament, pharmaceutical composition or vaccine as claimed in claim 32 further comprising a pharmaceutically acceptable carrier, adjuvant or diluent.

34. (Currently Amended) An oncolytic herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase (NTR) and wherein said nucleic acid sequence is in at least one of the long repeat regions (R_L) or wherein said herpes sirnplex virus is non-neurovirulent,

wherein the genome has an inactivating mutation in the RL1 locus such that the herpes simplex virus does not produce a functional ICP34.5 gene product,

and wherein the herpes simplex virus is a mutant of one of HSV-1 strains 17 or F or HSV-2 strain HG52.

35. (cancelled)

36. (Previously Presented) A composition comprising the herpes simplex virus of claim 34 and an NTR prodrug.

37. (Previously Presented) The composition as claimed in claim 36 wherein said NTR prodrug is CB1954.

38.-41. (cancelled)

42. (Previously Presented) A kit of parts comprising a first container having a quantity of herpes simplex virus of claim 1 and a second container having a quantity of an NTR prodrug.

43.-50. (cancelled)

51. (Withdrawn) A method for the treatment of a tumour comprising the steps of:

(i) administering to a patient in need of treatment a therapeutically effective amount of the herpes simplex virus of claim 1, wherein the genome of said virus comprises (a) a nucleic acid sequence encoding a nitroreductase in at least one of the long repeat regions (R_L), or (b) a nucleic acid sequence encoding a
nitroreductase and wherein the herpes simplex virus is non-neurovirulent; and

(ii) administering to said patient a therapeutically effective amount of an NTR prodrug.

52. (cancelled)

53. (Withdrawn) The method of claim 51 wherein said herpes simplex virus is capable of killing tumour cells.

54. (Withdrawn) The method as claimed in claim 51 wherein said NTR prodrug is CB1954.

55. (Withdrawn) A method of expressing in vitro or in vivo a nitroreductase, said method comprising the step of infecting at least one cell or tissue of interest with the herpes simplex virus of claim 1, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase in at least one of the long repeat regions (R_L), said nitroreductase operably linked to a transcription regulatory sequence.

56. (Withdrawn) A method of expressing in vitro or in vivo a nitroreductase, said method comprising the step of infecting at least one cell or tissue of interest with the herpes simplex virus of claim 1, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase, said nitroreductase operably linked to a transcription regulatory sequence, and wherein the herpes simplex virus is non-neurovirulent.

57. (Previously Presented) Herpes simplex virus HSV1716/CMV-NTR/GFP (ECACC accession number 03110501).

58. (Withdrawn) A method for the treatment of a tumour comprising administering to a patient in need of treatment a therapeutically effective amount of the herpes simplex virus of claim 1.

59. (Withdrawn) A method for the treatment of a tumour comprising administering to a patient in need of treatment a therapeutically effective amount of the herpes simplex virus of claim 34.

60. (Previously Presented) A medicament, pharmaceutical composition or vaccine comprising the herpes simplex virus of claim 34.

61. (Previously Presented) The medicament, pharmaceutical composition or vaccine as claimed in claim 60 further comprising a pharmaceutically acceptable carrier, adjuvant or diluent.

62. (Previously Presented) A kit of parts comprising a first container having a quantity of herpes simplex virus of claim 34 and a second container having a quantity of an NTR prodrug.

63. (Previously Presented) The kit as claimed in claim 42 wherein said NTR prodrug is CB1954.

64. (Previously Presented) The kit as claimed in claim 62 wherein said NTR prodrug is CB1954.

65. (New) The herpes simplex virus of claim 1, wherein the herpes simplex virus genome comprises nucleic acid encoding an heterologous NTR, wherein the genome has an inactivating mutation in the RL1 locus such that the herpes simplex virus does not produce a functional ICP34.5 gene product, and wherein the genome of the herpes simplex virus otherwise substantially resembles the genome of HSV-1 strain 17 or F or HSV-2 strain HG52.

66. (New) The herpes simplex virus of claim 1, wherein the herpes simplex virus genome comprises nucleic acid encoding an heterologous NTR, wherein the genome has an inactivating mutation in the RL1 locus such that the herpes simplex virus does not produce a functional ICP34.5 gene product, and wherein the genome of the herpes simplex virus otherwise is the genome of HSV-1 strain 17 or F or HSV-2 strain HG52.

67. (New) The herpes simplex virus of claim 1, wherein the herpes simplex virus genome comprises nucleic acid encoding an heterologous NTR, wherein the herpes simplex virus genome has an inactivating mutation in the RL1 locus such that the herpes simplex virus does not produce a functional ICP34.5 gene product, wherein the herpes simplex virus genome has a mutation in the ribonucleotide reductase gene, and wherein the herpes simplex genome otherwise substantially resembles the genome of HSV-1 strain 17 or F or HSV-2 strain HG52.

68. (New) The herpes simplex virus of claim 1, wherein the herpes simplex virus genome comprises nucleic acid encoding an heterologous NTR, wherein the herpes simplex virus genome has an inactivating mutation in the RL1 locus such that the herpes simplex virus does not produce a functional ICP34.5 gene product, wherein the herpes simplex virus genome has a mutation in the ribonucleotide reductase gene, and wherein the herpes simplex genome otherwise is the genome of HSV-1 strain 17 or F or HSV-2 strain HG52.

69. (New) The herpes simplex virus of claim 1, wherein the herpes simplex virus is a mutant of HSV-1 strain 17 or F.

70. (New) The herpes simplex virus of claim 1, wherein all copies of the ICP34.5 gene present in the herpes simplex virus genome are disrupted such that the herpes simplex virus is incapable of producing a functional ICP34.5 gene product.